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**(54) Title:** TRANSDERMAL ADMINISTRATION OF OLANZAPINE**(57) Abstract**

Transdermal administration of olanzapine and pharmaceutically acceptable acid addition salts thereof is described. The method involves treating an individual suffering from or susceptible to psychosis, acute mania or mild anxiety states, particularly those afflicted with schizophrenia or schizophreniform illnesses, by administering olanzapine or a salt thereof through the skin or mucosal tissue, for a time period and at an administration rate effective to alleviate the symptoms of the disease. Pharmaceutical formulations and drug delivery systems for administering olanzapine are provided as well.

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TRANSDERMAL ADMINISTRATION OF OLANZAPINETechnical Field

This invention relates generally to transdermal drug delivery, and more particularly 10 relates to methods and drug delivery systems for administering olanzapine transdermally. The invention additionally relates to pharmaceutical compositions formulated for transdermal administration of olanzapine.

15

Background

The delivery of drugs through the skin provides many advantages; primarily, such a means of delivery is a comfortable, convenient and noninvasive 20 way of administering drugs. The variable rates of absorption and metabolism encountered in oral treatment are avoided, and other inherent inconveniences -- e.g., gastro-intestinal irritation and the like -- are eliminated as well. Transdermal 25 drug delivery also makes possible a high degree of control over blood concentrations of any particular drug.

Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment 30 into and through intact skin must first penetrate the stratum corneum. They must then penetrate the viable epidermis, the papillary dermis, and the capillary walls into the blood stream or lymph channels. To be so absorbed, molecules must overcome a different 35 resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex phenomenon. However, it is the cells of the stratum

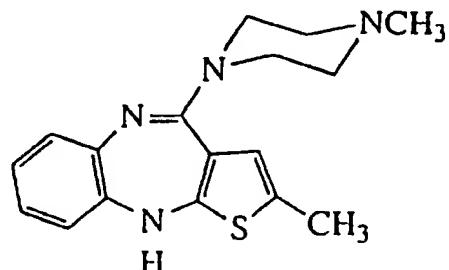
corneum which present the primary barrier to absorption of topical compositions or transdermally administered drugs. The stratum corneum is a thin layer of dense, highly keratinized cells approximately

5 10-15 microns thick over most of the body. It is believed to be the high degree of keratinization within these cells as well as their dense packing which creates in most cases a substantially impermeable barrier to drug penetration.

10 Relatively recent advances in transdermal drug delivery have enabled effective administration of a variety of drugs through the skin. These advances include the development of a number of skin penetration enhancing agents, or "permeation 15 enhancers," to increase skin permeability, as well as non-chemical modes for facilitating transdermal delivery, e.g., the use of iontophoresis, electroporation or ultrasound. Nevertheless, the number of drugs that can be safely and effectively 20 administered through the skin, without concomitant problems such as irritation or sensitization, remains limited.

The present invention is directed to the transdermal administration of 2-methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine, also known as "olanzapine." The drug is described in U.S. Patent No. 5,229,382 to Chakrabarti et al., issued July 20, 1993, and assigned to Lilly Industries Limited. Reference may be had thereto for any 30 information concerning methods for synthesizing or using olanzapine not explicitly included herein.

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10

Olanzapine

Olanzapine is an antagonist of dopamine at the D-1 and D-2 receptors, and in addition has antimuscarinic

15 anticholinergic properties and antagonist activity at 5HT-2 receptor sites and at noradrenergic  $\alpha$ -receptors (Moore et al., *J. Pharmacol. Exp. Ther.* **262**(2):545-551 (1992)). The drug has relaxant, anxiolytic and anti-emetic properties, and, as explained in the  
20 Chakrabarti et al. patent referenced above, is useful in the treatment of psychosis, acute mania and mild anxiety states, and is particularly useful in the treatment of schizophrenia and schizophreniform illnesses.

25 Earlier methods for treating schizophrenia typically involved the use of the antipsychotic agents haloperidol, clozapine and flumezapine (7-fluoro-2-methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]-benzodiazepine). However, as explained in  
30 U.S. Patent No. 5,229,382 to Chakrabarti et al., these drugs were problematic in a number of ways. Haloperidol was found to cause a high incidence of extra pyramidal symptoms, e.g., Parkinsonism, acute dystonic reactions, akathisia, tardive dyskinesia and  
35 tardive dystonia. While clozapine was claimed to be substantially free of such extra pyramidal symptoms, it was found to cause agranulocytosis in some

patients, a condition resulting in a lowered white blood cell count to a potentially life-threatening degree. Flumazepine was found to result in still additional problems, leading to termination of 5 clinical trials before commercialization, the problems primarily related to an unacceptably high levels of certain enzymes, e.g., creatinine phosphokinase, serum glutamate oxalacetic transaminase and serum glutamate pyruvate transaminase. A related drug, 10 chlorpromazine, has also been found to give rise to a number of problems.

Olanzapine has been developed as a drug which is highly effective in the treatment of psychosis, acute mania and mild anxiety states. 15 Olanzapine has been found to be a very safe and effective antipsychotic agent which does not appear to give rise to extra pyramidal symptoms, agranulocytosis, or unacceptably high enzyme levels. Olanzapine has been established to be more potent than 20 clozapine in blocking 5HT2 and dopamine-D2 in studies in rodents (Fuller et al., *Research Communications in Chemical and Pathology and Pharmacology* 77:1187-1193 (1992)). Additionally, in Phase II, double-blind, randomized, placebo controlled clinical trials, it was 25 concluded that olanzapine is effective in treating both the positive and negative symptoms of schizophrenia and is well-tolerated (P.V. Tran et al., *Neuropsychopharmacology* 10(3):267S, suppl., pt. 2 (1994)).

30 Currently, olanzapine is administered orally or by injection. While, as alluded to above, the drug is an extremely effective antipsychotic agent, drug non-compliance is a serious problem, and is believed to account for approximately one-third of all short-stay hospital costs. Transdermal administration of 35 olanzapine, as disclosed and claimed herein, significantly enhances patient compliance by providing

an advanced delivery system useful for administering the drug over an approximately three- to seven-day period.

There are a number of other advantages to

5 administering olanzapine transdermally as well: gastrointestinal and other side effects associated with oral administration are substantially avoided; continuous delivery provides for sustained blood levels; the transdermal patch is easily removable if

10 any side effects do occur; and the likelihood of patient acceptance is significantly improved. In general, steady-state, transdermal delivery of the drug seems to provide a far better side effect profile overall than is associated with oral administration.

15 None of the art of which applicants are aware describes a transdermal drug delivery system for administering olanzapine. Nor does the art set forth data on skin permeability or therapeutic administration rates with respect to such compounds.

20 To the best of applicants' knowledge, then, the transdermal administration of olanzapine is unknown and completely unsuggested by the art.

Disclosure of the Invention

25 Accordingly, it is a primary object of the present invention to address the above-mentioned need in the art by providing methods, pharmaceutical formulations and systems for the transdermal administration of olanzapine or a pharmaceutically acceptable acid addition salt thereof.

It is another object of the invention to provide a method for treating psychosis, acute mania or mild anxiety states, particularly schizophrenia or schizophreniform illnesses, by administering

35 olanzapine or a pharmaceutically acceptable acid addition salt thereof through a predetermined area of intact skin or mucosal tissue for a time period and at

an administration rate effective to alleviate the symptoms at issue.

It is still another object of the invention to provide such a method which involves the  
5 transdermal administration of a pharmaceutically acceptable acid addition salt of olanzapine.

It is a further object of the invention to provide such a method in which olanzapine or a pharmaceutically acceptable acid addition salt thereof  
10 is administered in conjunction with a skin permeation enhancer.

It is a further object of the invention to provide olanzapine-containing compositions formulated for transdermal delivery.

15 It is still a further object of the invention to provide a "solid matrix" type transdermal system for administering olanzapine as provided herein which comprises a laminated composite of a backing layer and a contact adhesive layer which contains the  
20 drug and serves as the basal surface which contacts the skin or mucosal tissue during use.

It is yet a further object of the invention to provide a transdermal system for administering olanzapine as provided herein which comprises a  
25 laminated composite of a backing layer, a contact adhesive layer which serves as the basal surface and contacts the skin or mucosal tissue during use, and, incorporated therebetween, a polymeric matrix which contains the drug and serves as the drug reservoir.

30 It is still a further object of the invention to provide a transdermal system for administering olanzapine as provided herein, in the form of a patch having an internal reservoir of a liquid, gel or foam with the drug dispersed or adsorbed therein.

Still further objects of the invention are to provide transdermal systems for administering

olanzapine, containing high capacity polyurethane hydrogel drug reservoirs or reservoirs of superabsorbent material as will be described elsewhere herein.

5           Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the  
10         invention.

In one aspect of the invention, a method is provided for treating an individual suffering from or susceptible to psychosis, acute mania or mild anxiety states, particularly schizophrenia and

15         schizophreniform illnesses, by transdermally administering a therapeutically effective amount of olanzapine or a pharmaceutically acceptable acid addition salt thereof, for a time period and at an administration rate effective to alleviate the  
20         symptoms at issue. The method is premised on the discovery that olanzapine and pharmaceutically acceptable salts thereof may be administered through the skin or mucosal tissue to achieve desired systemic effects. In a preferred embodiment, a skin permeation  
25         enhancer is coadministered with the drug so as to increase permeability thereto and achieve more rapid delivery.

It should be noted that while the present invention is directed to the treatment of individuals  
30         suffering from or susceptible to psychosis, acute mania or mild anxiety states, and is particularly useful in the treatment of schizophrenia or schizophreniaform illnesses, the present method may extend to any use of olanzapine deriving from its  
35         activity an antagonist of dopamine at the D-1 and D-2 receptors, its antimuscarinic anti-cholinergic

properties, and/or its antagonist activity at 5HT-2 receptor cites and noradrenergic  $\alpha$ -receptors.

In another aspect of the invention, a therapeutic system for transdermal administration of 5 olanzapine is provided. The system is a laminated composite comprising a backing layer, a drug reservoir, and a means for affixing the composite to the skin. The drug reservoir and the affixing means may be distinct, such that a separate contact adhesive 10 layer is provided which serves as the basal surface of the device, or the drug reservoir may itself be comprised of an adhesive layer which is suitable for contacting and adhering to the skin. Such therapeutic systems are in the nature of "solid matrix" type 15 transdermal patches. Alternative systems, containing the drug in a liquid, gel or foam reservoir, may, however, be used as well. The transdermal system is preferably constructed such that an effective dose of olanzapine or a pharmaceutically acceptable acid 20 addition salt thereof will be delivered for a period in the range of about three to seven days.

Brief Description of the Drawings

FIG. 1 illustrates in schematic form one 25 embodiment of a solid matrix-type transdermal delivery system which may be used in conjunction with the present invention.

FIG. 2 illustrates in schematic form an alternative embodiment of a solid matrix-type 30 transdermal delivery system which may be used in conjunction with the present invention.

FIG. 3 illustrates in schematic form a liquid reservoir-type transdermal delivery system 35 which may be used in conjunction with the present invention.

FIGS. 4-13 are graphs illustrating olanzapine flux obtained using various vehicles and prototypes, as described in the Examples herein.

5    Modes for Carrying Out the Invention

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular formulations or transdermal systems as such may, of course, vary. It is also to 10 be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular 15 forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a permeation enhancer" includes a mixture of two or more permeation enhancers, reference to "an excipient" or "a vehicle" 20 includes mixtures of excipients or vehicles, reference to "an adhesive layer" includes reference to two or more such layers, and the like.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as 25 commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the preferred 30 materials and methods are described herein.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

By "transdermal" delivery, applicants intend 35 to include both transdermal (or "percutaneous") and transmucosal administration, i.e., delivery by passage

of a drug through the skin or mucosal tissue and into the bloodstream.

By "therapeutically effective" amount is meant a nontoxic but sufficient amount of a compound

5 to provide the desired therapeutic effect, in the present case, that dose of olanzapine which will be effective in relieving or preventing symptoms of psychosis, acute mania, mild anxiety, or the like. An "effective" amount of a permeation enhancer as used  
10 herein means an amount that will provide the desired increase in skin permeability and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

By "predetermined area of skin" is intended

15 a defined area of intact unbroken living skin or mucosal tissue. That area will usually be in the range of about 1 cm<sup>2</sup> to about 100 cm<sup>2</sup>, more usually in the range of about 20 cm<sup>2</sup> to about 60 cm<sup>2</sup>. However, it will be appreciated by those skilled in the art of  
20 transdermal drug delivery that the area of skin or mucosal tissue through which drug is administered may vary significantly, depending on patch configuration, dose, and the like.

When transdermal administration of

25 "olanzapine" per se is indicated herein, it is to be understood that the described method, formulation or system extends to pharmaceutically acceptable acid addition salts as well.

"Penetration enhancement" or "permeation

30 enhancement" as used herein relates to an increase in the permeability of skin to a pharmacologically active agent, i.e., so as to increase the rate at which the drug permeates through the skin and enters the bloodstream. The enhanced permeation effected through  
35 the use of such enhancers can be observed by measuring the rate of diffusion of drug through animal or human

skin using a diffusion cell apparatus as described in the Examples herein.

"Carriers" or "vehicles" as used herein refer to carrier materials suitable for transdermal drug administration, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with other components of the composition in a deleterious manner.

5 Examples of suitable carriers for use herein include water, silicone, liquid sugars, waxes, petroleum jelly, and a variety of other materials. The term "carrier" or "vehicle" as used herein may also refer to stabilizers, crystallization inhibitors, or other 10 types of additives useful for facilitating transdermal 15 drug delivery.

The present method of transdermally delivering olanzapine may vary, but necessarily involves application of a composition containing olanzapine or a pharmaceutically acceptable acid addition salt thereof to a predetermined area of the skin or mucosal tissue for a period of time sufficient to provide an effective blood level of drug for a desired period of time. The method may involve direct 20 application of the composition as an ointment, gel, cream, or the like, or may involve use of a drug delivery device as taught in the art, e.g., in 25 commonly assigned U.S. Patent Nos. 4,915,950, 4,906,463, 5,091,186 or 5,246,705, or as described 30 below.

As noted above, olanzapine may be administered as the base or in the form of a pharmaceutically acceptable acid addition salt. As will be appreciated by those skilled in the art, the 35 base form of the drug can be converted to an acid addition salt by treatment with a stoichiometric excess of a selected acid. Such acid addition salts

may be formed, for example, with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with organic acids such as acetic acid, propionic acid,  
5 glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, hydroxymaleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-  
10 toluenesulfonic acid, naphthalene-2-sulfonic acid, salicylic acid and the like.

It will generally be necessary to administer olanzapine or an acid addition salt thereof in conjunction with a permeation enhancer. Suitable  
15 enhancers include, but are not limited to, dimethylsulfoxide (DMSO), dimethyl formamide (DMF), N,N-dimethylacetamide (DMA), decylmethylsulfoxide ( $C_{10}$ MSO), polyethylene glycol monolaurate (PEGML), propylene glycol (PG), propylene glycol monolaurate  
20 (PGML), glycerol monolaurate (GML), methyl laurate (ML), lauryl lactate (LL), isopropyl myristate (IPM), terpenes such as menthone,  $C_2$ - $C_6$  alkanediols, particularly 1,2-butanediol, lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-  
25 dodecylcyclazacycloheptan-2-one (available under the trademark Azone® from Whitby Research Incorporated, Richmond, VA), alcohols, and the like. Vegetable oil permeation enhancers such as safflower oil, cotton seed oil and corn oil may also be used, as described  
30 in commonly assigned U.S. Patent No. 5,229,130 to Sharma.

One group of preferred enhancers for use in conjunction with the transdermal administration of olanzapine and acid addition salts thereof are esters given by the formula  $[CH_3(CH_2)_mCOO]_nR$  in which m is an integer in the range of 8 to 16, n is 1 or 2, and R is a lower alkyl ( $C_1$ - $C_3$ ) residue that is either  
35

unsubstituted or substituted with one or two hydroxyl groups. In the preferred embodiment herein, the ester component is a lower alkyl ( $C_1-C_3$ ) laurate (i.e.,  $m$  is 10 and  $n$  is 1), and in a particularly preferred case

5 is "PGML." It will be appreciated by those skilled in the art that the commercially available material sold as "PGML" is typically a mixture of propylene glycol monolaurate itself, propylene glycol dilaurate, and either propylene glycol, methyl laurate, or both.

10 Thus, the terms "PGML" or "propylene glycol monolaurate" as used herein are intended to encompass both the pure compound as well as the mixture that is typically obtained commercially.

Also preferred are fatty acids and fatty  
15 alcohols corresponding to the above-defined fatty esters. Thus, fatty acids useful as permeation enhancers herein will generally have the formula  $CH_3(CH_2)_mCOOH$ , where  $m$  is as above, while the fatty alcohols will have the formula  $CH_3(CH_2)_mCH_2OH$ .

20 Other preferred enhancer compositions are wherein a fatty ester as described above is combined with an ether component selected from the group consisting of diethylene glycol monoethyl ether and diethylene glycol monomethylether. Such enhancer  
25 compositions are described in U.S. Patent Nos. 5,053,227 and 5,059,426 to Chiang et al., both of common assignment herewith.

Particularly preferred permeation enhancers  
30 are selected from the group consisting of  $C_2-C_6$  alkanediols, fatty esters having the structural formula  $[CH_3(CH_2)_mCOO]_nR$ , fatty acids having the structural formula  $CH_3(CH_2)_mCOOH$ , fatty alcohols having the structural formula  $CH_3(CH_2)_mCH_2OH$ , and mixtures thereof.

35 The amount of enhancer present in the composition will similarly depend on a number of factors, e.g., the strength of the particular

enhancer, the desired increase in skin permeability, rate of administration, and amount of drug delivered.

The drug reservoir used in a transdermal system for administering olanzapine will generally

5 comprise on the order of 20 wt.% to 80 wt.% reservoir material (e.g., adhesive polymer, hydrogel, or the like), with the remainder of the reservoir comprised of drug formulation, i.e., olanzapine, enhancer, and any carriers or vehicles which may be used.

10 Typically, although not necessarily, the drug formulation will contain on the order of 1 wt.% to 20 wt.% olanzapine and, correspondingly, 80 wt.% to 99 wt.% enhancer and other vehicles. In this way, the composition may be optimized to produce a transdermal 15 system capable of delivering olanzapine over an approximately three- to seven-day period (with patches worn for longer periods generally corresponding to lower dose systems).

20 One type of transdermal system for transdermally administering an indolone compound of Formula (I) is "solid matrix" type system shown in FIG. 1. The composite, generally designated 10, comprises a backing layer 11, a reservoir layer 12 containing drug 12a either dispersed therein, or 25 adsorbed or absorbed by a particulate hydrophilic material, and a release liner 13.

20 The backing layer 11 functions as the primary structural element of the device and provides the device with much of its flexibility, drape and, preferably, occlusivity. The material used for the backing layer should be inert and incapable of absorbing drug, enhancer or other components of the pharmaceutical composition contained within the device. The backing is preferably made of one or more sheets or films of a flexible elastomeric material 35 that serves as a protective covering to prevent loss of drug and/or vehicle via transmission through the

upper surface of the device, and will preferably impart a degree of occlusivity to the device, such that the area of the skin covered on application becomes hydrated. The material used for the backing 5 layer should permit the device to follow the contours of the skin and be worn comfortably on areas of skin such as at joints or other points of flexure, that are normally subjected to mechanical strain with little or no likelihood of the device disengaging from the skin 10 due to differences in the flexibility or resiliency of the skin and the device. Examples of materials useful for the backing layer are polyesters, polyethylene, polypropylene, polyurethanes and polyether amides. The layer is preferably in the range of about 15 15 microns to about 250 microns in thickness, and may, if desired, be pigmented, metallized, or provided with a matte finish suitable for writing.

The reservoir layer 12 in FIG. 1 doubles as the means for containing drug and as an adhesive for 20 securing the device to the skin during use. That is, as release liner 13 is removed prior to application of the device to the skin, reservoir layer 12 serves as the basal surface of the device which adheres to the skin. Reservoir layer 12 is comprised of a pressure- 25 sensitive adhesive suitable for long-term skin contact. It must also be physically and chemically compatible with olanzapine or the acid addition salt thereof, and the carriers and vehicles employed. The reservoir layer will generally range in thickness from 30 about 1 to about 100 microns, preferably in the range of approximately 20 to 75 microns. Suitable materials for this layer include, for example, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low 35 molecular weight polyether amide block polymers (e.g., PEBAX), tacky rubbers such as polyisobutene, polystyrene-isoprene copolymers, polystyrene-butadiene

copolymers, and mixtures thereof. Presently preferred adhesive materials for use as reservoir layer 12 are acrylates, silicones and polyurethanes.

Release liner 13 is a disposable element  
5 which serves to protect the device prior to application. Typically, the release liner is formed from a material impermeable to the drug, vehicle and adhesive, and which is easily stripped from the contact adhesive. Release liners are typically  
10 treated with silicone or fluorocarbons. Silicone-coated polyester is presently preferred.

In a variation on this embodiment, reservoir layer 12 comprises a matrix of a continuous hydrophobic polymer phase, with a particulate phase of  
15 a hydrated inorganic silicate and drug adsorbed or absorbed thereby. Such a system is described, for example, in PCT Publication No. WO94/07468, entitled "Two-Phase Matrix for Sustained Release Drug Delivery Device." As explained therein, polymers which may be  
20 used as the continuous hydrophobic phase are polysiloxanes, polyisobutylene, solvent-based hydrophobic polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether block amide copolymers, styrene-  
25 butadiene polymers, and vinyl acetate-based adhesives, with the hydrophobic polymer normally constituting about 30 wt.% to 95 wt.%, more typically 40 wt.% to 60 wt.%, of the matrix. The dispersed inorganic silicate is in the form of particulates that are typically in  
30 the non-colloidal size range of 0.001 to 0.1 mm, more usually 0.01 to 0.05 mm.

Preferably, the matrix in this embodiment additionally contains a dispersing agent which aids in maintaining the particulate phase dispersed in the  
35 continuous phase. Anionic, cationic, amphoteric or nonionic dispersing agents may be used. Preferably, the dispersing agent is a non-ionic surfactant such as

a polyethylene-polyoxypropylene glycol copolymer (e.g., that commercially available under the "Pluronic" trademark) or a polyoxyethylene sorbitan ester (e.g., that commercially available under the 5 "Tween" trademark); the dispersing agent will normally constitute about 0.5 wt.% to 10 wt.% of the matrix, more usually 3 wt.% to 6 wt.% of the matrix.

These matrices are prepared by dissolving the drug in water (with, optionally, additional 10 hydrophilic polar solvents) and contacting the hydrophilic particulate material with the resulting solution to permit the aqueous solution to be absorbed by the particulate material. The mixture will typically have the texture of a paste. The 15 hydrophobic components of the matrix and the dispersing agent, preferably in admixture, are added to the paste with vigorous mixing to form a viscous dispersion. This dispersion may be formed into appropriate shapes and excess solvent removed 20 therefrom.

FIG. 2 illustrates a different type of laminated composite that may serve as the transdermal delivery system herein. That system is shown generally at 14, with backing layer 15, drug reservoir 25 16, contact adhesive layer 17, and release liner 18. The backing layer and release liner are as described above with respect to the structure of FIG. 1. With regard to drug reservoir 16 and contact adhesive layer 17, suitable materials are as described above, e.g., 30 polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether amide block polymers, tacky rubbers, and mixtures thereof.

FIG. 3 depicts an alternative device 35 structure for administering olanzapine or a salt thereof transdermally. The device is a "liquid reservoir" type and is generally designated 18. It

comprises a top, impermeable backing layer 19, an underlying liquid, gel (e.g., a hydrogel as described below) or foam layer 20, generally a liquid layer, containing the drug and any associated materials, 5 e.g., enhancers or the like, that is sealed at its edge to the overlying backing layer to form a pouch between the backing and the underlying modulator layer 21, and a pressure-sensitive adhesive layer 22 that serves as the basal surface of the device and affixes 10 the device to the skin during use. The modulator layer is generally a thin, flexible layer of a highly porous material such as polyester, polyethylene, polypropylene, or the like. As with the above embodiments, the device of FIG. 3 is provided with a 15 release liner (not shown) to protect adhesive layer 22 prior to use. Such devices are described, for example, in commonly assigned U.S. Patent No. 5,124,157 to Colley et al.

Such transdermal drug delivery systems for 20 use in conjunction with the administration of olanzapine or salts thereof can be fabricated using conventional techniques which are within the skill of the art, and/or explained in the literature. In general, devices of the invention are fabricated by 25 solvent evaporation film casting, thin film lamination, die cutting, or the like.

Particularly preferred transdermal systems for administering olanzapine are those containing high capacity drug reservoirs such as may be fabricated 30 from polyurethane hydrogels or from "superabsorbent" materials.

Briefly, transdermal systems containing high capacity, polyurethane hydrogel reservoirs are fabricated by crosslinking a polyurethane with a 35 catalyst in the presence of water, or by photocuring in the presence of photoinitiator, in the presence of water. Drug formulation is incorporated into the

hydrogel so formed, either during or after manufacture. It is preferred that the hydrogel be fabricated such that the polyurethane starting material is crosslinked with an aliphatic, 5 cycloaliphatic or aromatic diisocyanate in the presence of water, and that the drug formulation be absorbed therein following hydrogel formation. A laminated composite, containing the drug-containing hydrogel reservoir, a backing layer, optional 10 additional layers such as a contact adhesive layer and a rate-controlling membrane, is then prepared, to serve as the delivery system to be affixed to the skin or mucosal tissue.

Drug reservoirs fabricated from 15 superabsorbent materials are typically comprised of crosslinked polymers capable of absorbing at minimum 15 g drug formulation per g superabsorbent material (although polymers capable of absorbing far greater quantitites of drug formulation may be used as well). 20 Examples of such superabsorbent materials are olefin/alkyl carboxylate copolymers, e.g., maleic anhydride-isobutylene copolymer, although other superabsorbent materials may also be used. As with the hydrogel-based systems, a laminated composite may 25 be prepared using conventional techniques, and serves as the transdermal drug delivery system.

In any of these transdermal systems, it may be desirable to include a rate-controlling membrane between the drug reservoir and a contact adhesive 30 layer, when one is present. The materials used to form such a membrane are selected to limit the flux of non-drug components, i.e., enhancers, vehicles, and the like, from the drug reservoir, while not limiting the flux of drug. Representative materials useful for 35 forming rate-controlling membranes include polyolefins such as polyethylene and polypropylene, polyamides, polyesters, ethylene-ethacrylate copolymer, ethylene-

v vinyl acetate copolymer, ethylene-vinyl methylacetate copolymer, ethylene-vinyl ethylacetate copolymer, ethylene-vinyl propylacetate copolymer, polyisoprene, polyacrylonitrile, ethylene-propylene copolymer, and  
5 the like. A particularly preferred material useful to form the rate controlling membrane is ethylene-vinyl acetate copolymer.

---

10 It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the description above as well as the examples which follow are intended to illustrate and not limit the scope of  
15 the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

In the following examples, efforts have been  
20 made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental error and deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C and pressure is at or near atmospheric.

25

Experimental

Materials and Methods:

30 Olanzapine free base was provided by Eli Lilly. All chemicals were reagent grade.

In Vitro Skin Permeation of Olanzapine:

Skin Preparation: Human cadaver skin was  
used for the permeation studies. The frozen skins  
35 were thawed and the epidermal layers (stratum corneum and viable epidermis) were separated from the full-thickness skin by immersing it in water at 60°C for

two min. This epidermis was either used immediately for flux studies or stored at -20°C for later studies.

Skin permeation from vehicles: Modified

Franz diffusion cells were used for evaluating the

5 performance of vehicles for olanzapine delivery. The receiver compartment was filled with 7.5 ml of pH 7.4 buffer. Quantities ranging from 200 to 500 µl of the selected vehicles saturated with olanzapine were then placed into the donor compartment to initiate the skin  
10 flux experiments. The temperature of the diffusion cell contents was maintained at 32°C ± 1°C. At predetermined times, the entire receiver content was withdrawn and replaced with fresh buffer. Samples were assayed by HPLC.

15 Skin permeation from prototypes: Modified

Franz cells were used for evaluating the prototype systems for delivery of olanzapine. The prototype systems were peeled off the polyester release liner and placed on top of the epidermis with the drug

20 adhesive layer facing the stratum corneum. Gentle pressure was applied to insure full contact between the drug adhesive layer and the stratum corneum. The skin membrane with the olanzapine prototype system was then mounted carefully between the donor and the

25 receiver compartments. The receiver compartment was filled with pH 7 buffer and the temperature was maintained at 32°C ± 1°C throughout the experimental period. The entire receiver content was withdrawn and replaced with fresh buffer. Samples were assayed by  
30 HPLC.

Flux determination: Skin flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) was determined from the steady-state slope of the plot of the cumulative amount of olanzapine permeated through the skin versus time. After steady state had been established, the linear portion of the plot was used to calculate the flux from the slope. For some formulations, the steady state was not achieved, and

the data were plotted as flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) at each time point (dividing the quantity penetrating the skin during each time period, corrected for surface area by the time of penetration through the skin). Each 5 formulation was run in triplicate, and the values reported represent the mean and standard deviation for three cells.

Skin Irritation Studies:

10 The primary skin irritation potential of olanzapine formulations were determined. A Draize irritation protocol was used, as follows. The backs of six rabbits were clipped free of hair, and six different test materials were applied in small Hilltop 15 chambers (0.2 ml) to the skin and worn for 24 hours. For the preliminary prototype, the system was applied to the rabbit skin, occluded using a release liner, and kept in place by means of an adhesive tape. The skin sites were scored according to the Draize scale 20 at 24, 48 and 72 hours after application of the test materials. Mean primary irritation scores are as follows. Range of values: 0, non-irritating; 0-1.9, mildly irritating; 2-5.9, moderately irritating; and 6-8.0, severely irritating

25

Example 1

Olanzapine was dissolved in a combination of two vehicles (as indicated in Table 1) and applied to human cadaver skin using a Franz diffusion cell. At 30 predetermined time intervals, as shown in FIGS. 4-8, the whole receiver fluid was replaced with fresh fluid and analyzed for olanzapine using HPLC method. The formulations are listed in Table 1 and the flux data are illustrated in graph form in FIGS. 4-8.

35

Table 1

| Formulation   |     |                                   |
|---|-----|-----------------------------------|
| 1.  | 90% | 1,2-butanediol + 10% PGML         |
| 5   | 2.  | 10% 1,2-butanediol + 90% PGML     |
|   | 3.  | 25% 1,2-butanediol + 75% PGML     |
|   | 4.  | 75% 1,2-butanediol + 25% PGML     |
|   | 5.  | 90% 1,2-butanediol + 10% LL       |
| 10  | 6.  | 10% 1,2-butanediol + 90% LL       |
|   | 7.  | 25% 1,2-butanediol + 75% LL       |
|   | 8.  | 75% 1,2-butanediol + 25% LL       |
|   | 9.  | 10% 1,2-butanediol + 90% LL       |
|   | 10. | 90% 1,2-butanediol + 10% IPM      |
| 15  | 11. | 25% 1,2-butanediol + 75% IPM      |
|   | 12. | 75% 1,2-butanediol + 25% IPM      |
|   | 13. | 100% ML                           |
|   | 14. | 10% 1,2-butanediol + 90% ML       |
| 20  | 15. | 90% 1,2-butanediol + 10% ML       |
|   | 16. | 25% 1,2-butanediol + 75% ML       |
|   | 17. | 90% 1,2-butanediol + 10% Menthone |
|   | 18. | 10% 1,2-butanediol + 90% Menthone |
|   | 19. | 25% 1,2-butanediol + 75% Menthone |
| 25  | 20. | 50% 1,2-butanediol + 50% Menthone |
| ML: Methyl Laurate, LL: Lauryl lactate, IPM: Isopropyl myristate. |     |                                   |

30

Example 2

Olanzapine was dissolved in a combination of three vehicles (as indicated in Table 2). The procedure of Example 1 was followed to evaluate *in vitro* flux. The formulations are listed in Table 2 and the results are shown in FIG. 9.

35

Table 2

| Formulation |   |
|-------------|---|
| 5           | 1. 10% Oleic acid + 45% PGML + 45% 1,2-butanediol   |
|             | 2. 10% Oleyl alcohol + 45% PGML + 45% 1,2-butanediol  |
|             | 3. 10% Methyl laurate + 45% Lauryl lactate + 45% 1,2-butanediol                                 |
| 10          | 4. 10% Lauric acid + 45% PGML + 45% 1,2-butanediol  |
|             | 5. 10% Lauric acid + 45% Methyl Laurate + 45% 1,2-butanediol                                    |
|             | 6. 10% Capric acid + 45% Lauryl lactate + 45% 1,2-butanediol                                    |
|             | 7. 10% Benzyl alcohol + 45% PGML + 45% 1,2-butanediol   |
| 15          | 8. 10% Oleic acid + 45% Methyl decanoate + 45% 1,2-butanediol 110                               |
|             | 9. 10% Capric acid + 90% Methyl Laurate   |
|             | ML: Methyl laurate; LL: Laurolactate; OA: Oleic acid;<br>TG: Thioglycerol; PG: Propylene glycol |

20

Example 3

Olanzapine was dissolved in a combination of vehicles (as indicated in Table 3) and absorbed onto a highly absorbent maleic anhydride-isobutylene copolymeric film, obtained from Concert Industries Limited, Thurso, Quebec, Canada. The systems were cut into  $1.25 \text{ cm}^2$  circles and applied onto the skin as in Example 1. The formulations are listed in Table 3 and the results are shown in FIG. 10.

25  
30

35

Table 3

| Formulation |   |
|-------------|---|
| 5           | 1. Saturated olanzapine in vehicle of 10% lauric acid + 45% Methyl laurate + 45% 1,2-butanediol adsorbed on two pieces 1.25 cm <sup>2</sup> each of superabsorbent film (Concert 100136 #95068) |
| 10          | 2. Saturated olanzapine in vehicle of 10% Oleyl alcohol + 45% PGML + 45% 1,2-butanediol adsorbed on two pieces 1.25 cm <sup>2</sup> each of superabsorbent film (Concert 100136 #95068)         |
| 15          | 3. Saturated olanzapine in vehicle of 10% Oleic acid + 45% Methyl caprate + 45% 1,2-butanediol adsorbed on two pieces 1.25 cm <sup>2</sup> each of superabsorbent film (Concert 100136 #95068)  |

Example 4

Olanzapine was dissolved in a combination of vehicles (see Table 4) and absorbed on a superabsorbent material as in Example 3. At the same time, a an ethylene vinyl acetate membrane was cut into 2 cm<sup>2</sup> circles and mounted onto the skin.

Following this procedure, the polymeric film having drug absorbed thereon was applied and the procedure of Example 1 was followed. The formulations are listed in Table 4 and the results are shown in FIG. 11.

Table 4

| Formulation |   |
|-------------|---|
| 30          | 1. Olanzapine saturated in 10% Lauric acid + 45% methyl Laurate + 45% 1,2-butanediol and absorbed on superabsorbent film (Concert 100136 with EVA 19%, 4 mil membrane). |
| 35          | 2. Olanzapine saturated in 10% Oleic acid + 45% methyl caprate + 45% 1,2-butanediol and absorbed on superabsorbent film (Concert 100136 with EVA 19%, 4 mil membrane).  |

Example 5

Olanzapine was dissolved in a combination of vehicles (see Table 5) and was added with water to Hypol® PreMA G-50 polymer (Hampshire Chemical Corporation) (ratio of water:polymer was approximately 2:1) and mixed together until a hydrogel was formed. The gel was cut into 2 cm<sup>2</sup> area circles and applied onto the skin as in Example 1. The formulations are listed in Table 5 and the results are shown in FIG.

10 12.

Table 5

| Formulation |   |
|-------------|---|
| 15 1.       | Hydrogel G-50 contains 25% Solution of saturated olanzapine in (10% Methyl Laurate + 45% Lauryl lactate + 45% 1,2-butanediol) |
| 2.          | Hydrogel G-50 contains 25% Solution of saturated olanzapine in (10% Lauric acid + 45% Lauryl lactate + 45% 1,2-butanediol)    |

20

Example 6

Olanzapine was dissolved in a combination of vehicles (as indicated in Table 6). Water was added to Hypol® PreMA G-50 polymer (Hampshire Chemical Corporation) (ratio of water:polymer was approximately 2:1) and mixed together until a hydrogel was formed. The gel was cut into 2 cm<sup>2</sup> circles which were then soaked with the olanzapine-vehicles combination overnight. The final product was applied onto the skin as in Example 1. The formulations are listed in Table 6 and the results are shown in FIG. 13.

| Table 6     |   |
|-------------|---|
| Formulation |   |
| 5           | 1. Olanzapine saturated in 10% Lauric acid + 45% methyl Laurate + 45% 1,2-butanediol and left overnight with Hypol PreMA gel. |
|             | 2. Olanzapine saturated in 10% Oleic acid + 45% methyl Caprate + 45% 1,2-butanediol and left overnight with Hypol PreMA gel.  |

10

Example 7

Results of the irritation studies conducted as explained above were as follows:

15

20

25

30

35

Table 7

## Primary Irritation Score (Draize Score)

|    | Formulation   | Draize Score |
|----|---|--------------|
| 5  | 1. Olanzapine saturated in PGML   | 2.3          |
| 10 | 2. Olanzapine saturated in 10% Oleyl alcohol + 45% Methyl Caprate + 45% 1,2-butanediol and absorbed on the superabsorbent and a membrane (EVA 19%) was put in between the skin and the superabsorbent | 1.4          |
| 15 | 3. Olanzapine saturated in 10% Oleic acid + 45% Methyl Caprate + 45% 1,2-butanediol and absorbed on the superabsorbent and a membrane (EVA 19%) was put in between the skin and the superabsorbent    | 1.4          |
| 20 | 4. Olanzapine saturated in 10% Lauric acid + 45% Methyl laurate + 45% 1,2-butanediol and absorbed on the superabsorbent and a membrane (EVA 19%) was put in between the skin and the superabsorbent   | 1.4          |
| 25 | 5. Olanzapine saturated in 10% Oleyl alcohol + 45% Methyl Caprate + 45% 1,2-butanediol in a Hypol PreMA G-50 Hydrogel   | 1.7          |
|    | 6. Olanzapine saturated in 10% Lauric acid + 45% Methyl Laurate + 45% 1,2-butanediol in a Hypol PreMA G-50 Hydrogel   | 2.2          |

As may be concluded from the results set forth in Table 7, irritation resulting from the formulations tested was minimal.

It may be concluded from these examples that sufficient skin fluxes of olanzapine can be achieved using any of a variety of enhancers, vehicles and prototypes, such that effective drug doses may be delivered using relatively small transdermal patches.

Claims:

1. A method for treating an individual suffering from or susceptible to psychosis, acute mania or mild anxiety, comprising transdermally administering to the individual a drug selected from the group consisting of olanzapine and pharmaceutically acceptable acid addition salts thereof, wherein the drug is administered such that the individual receives an effective daily dose over a three- to seven-day period.
2. The method of claim 1, wherein the drug is olanzapine base.
3. The method of claim 1, wherein the drug is a pharmaceutically acceptable acid addition salt of olanzapine.
4. The method of claim 1, wherein the drug is administered along with a skin permeation enhancer.
5. The method of claim 4, wherein the skin permeation enhancer is selected from the group consisting of C<sub>2</sub>-C<sub>6</sub> alkanediols, fatty esters having the structural formula [CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>COO]<sub>n</sub>R, fatty acids having the structural formula CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>COOH, fatty alcohols having the structural formula CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>CH<sub>2</sub>OH, and mixtures thereof.
6. A pharmaceutical formulation comprising a drug selected from the group consisting of olanzapine and pharmaceutically acceptable acid addition salts thereof, and a carrier and/or additive suitable for transdermal drug delivery.

7. The formulation of claim 6, wherein the drug is olanzapine base.

8. The formulation of claim 6, wherein the  
5 drug is a pharmaceutically acceptable olanzapine salt.

9. The formulation of claim 6, further  
including a skin permeation enhancer in an amount to  
facilitate permeation of drug through the skin at a  
10 therapeutically effective rate.

10. The method of claim 9, wherein the skin  
permeation enhancer is selected from the group  
consisting of C<sub>2</sub>-C<sub>6</sub> alkanediols, fatty esters having  
15 the structural formula [CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>COO]<sub>n</sub>R, fatty acids  
having the structural formula CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>COOH, fatty  
alcohols having the structural formula CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>CH<sub>2</sub>OH,  
and mixtures thereof.

20 11. A transdermal system for treating an  
individual suffering from or susceptible to psychosis,  
acute mania or mild anxiety, comprising a laminated  
composite of:

25 a backing layer that is substantially  
impermeable to the drug; and  
a reservoir layer having a drug formulation  
incorporated therein, wherein the drug formulation  
contains a drug selected from the group consisting of  
olanzapine and pharmaceutically acceptable acid  
30 addition salts thereof, and is present in the  
reservoir in an amount such that upon application of  
the system to the skin or mucosal tissue, the  
individual undergoing treatment receives an effective  
daily dose over an approximately three- to seven-day  
35 period.

12. The system of claim 11, wherein the reservoir layer is comprised of a pharmaceutically acceptable contact adhesive.

5 13. The system of claim 11, wherein the reservoir layer is comprised of a high capacity, polyurethane hydrogel.

10 14. The system of claim 11, wherein the reservoir layer is comprised of a superabsorbent crosslinked polymeric material.

15 15. The system of claim 11, wherein the drug is olanzapine base.

16. The system of claim 11, wherein the drug is a pharmaceutically acceptable olanzapine salt.

20 17. The system of claim 11, wherein the reservoir layer additionally comprises a skin permeation enhancer in an amount to facilitate permeation of drug through the skin at a therapeutically effective rate.

25 18. The method of claim 17, wherein the skin permeation enhancer is selected from the group consisting of C<sub>2</sub>-C<sub>6</sub> alkanediols, fatty esters having the structural formula [CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>COO]<sub>n</sub>R, fatty acids having the structural formula CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>COOH, fatty 30 alcohols having the structural formula CH<sub>3</sub>(CH<sub>2</sub>)<sub>m</sub>CH<sub>2</sub>OH, and mixtures thereof.

1 / 11

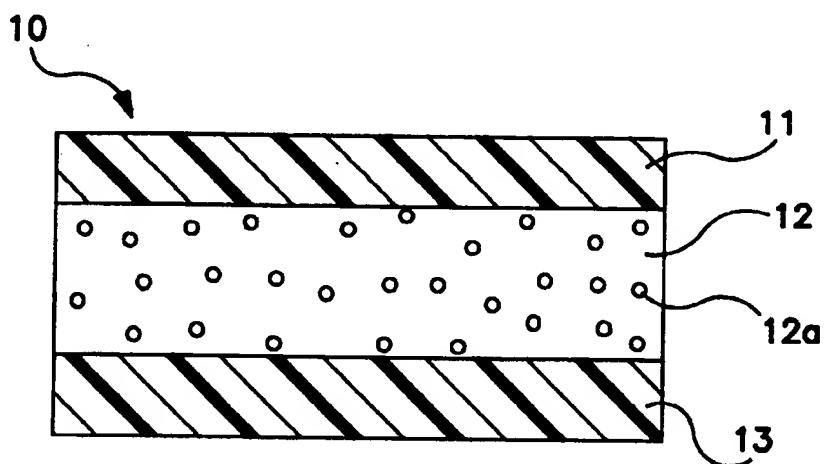


FIG. 1

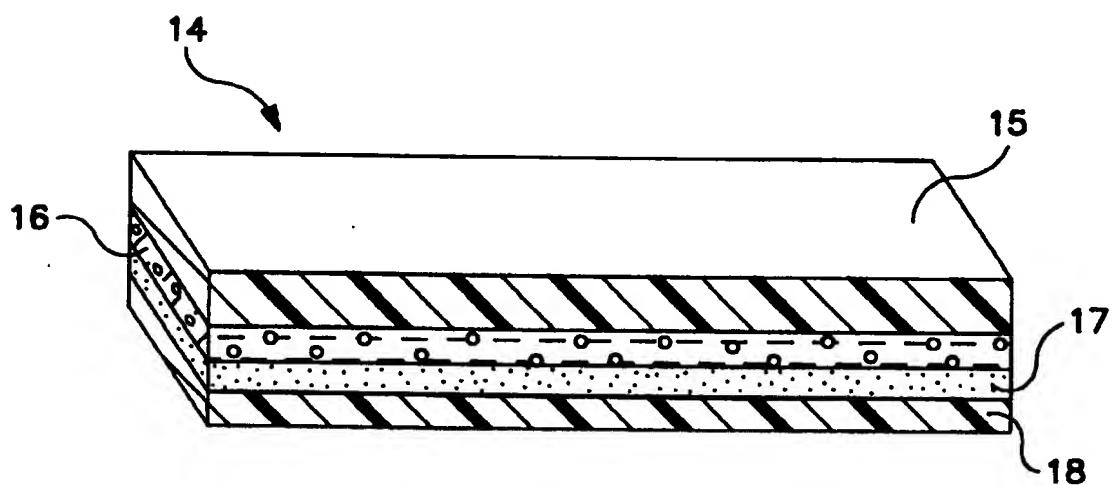


FIG. 2

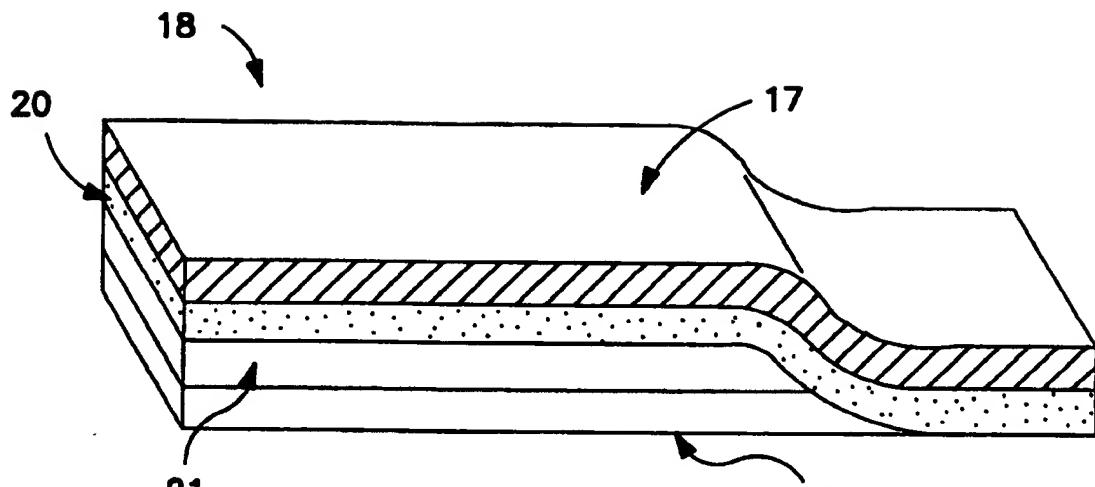


FIG. 3

2 / 11

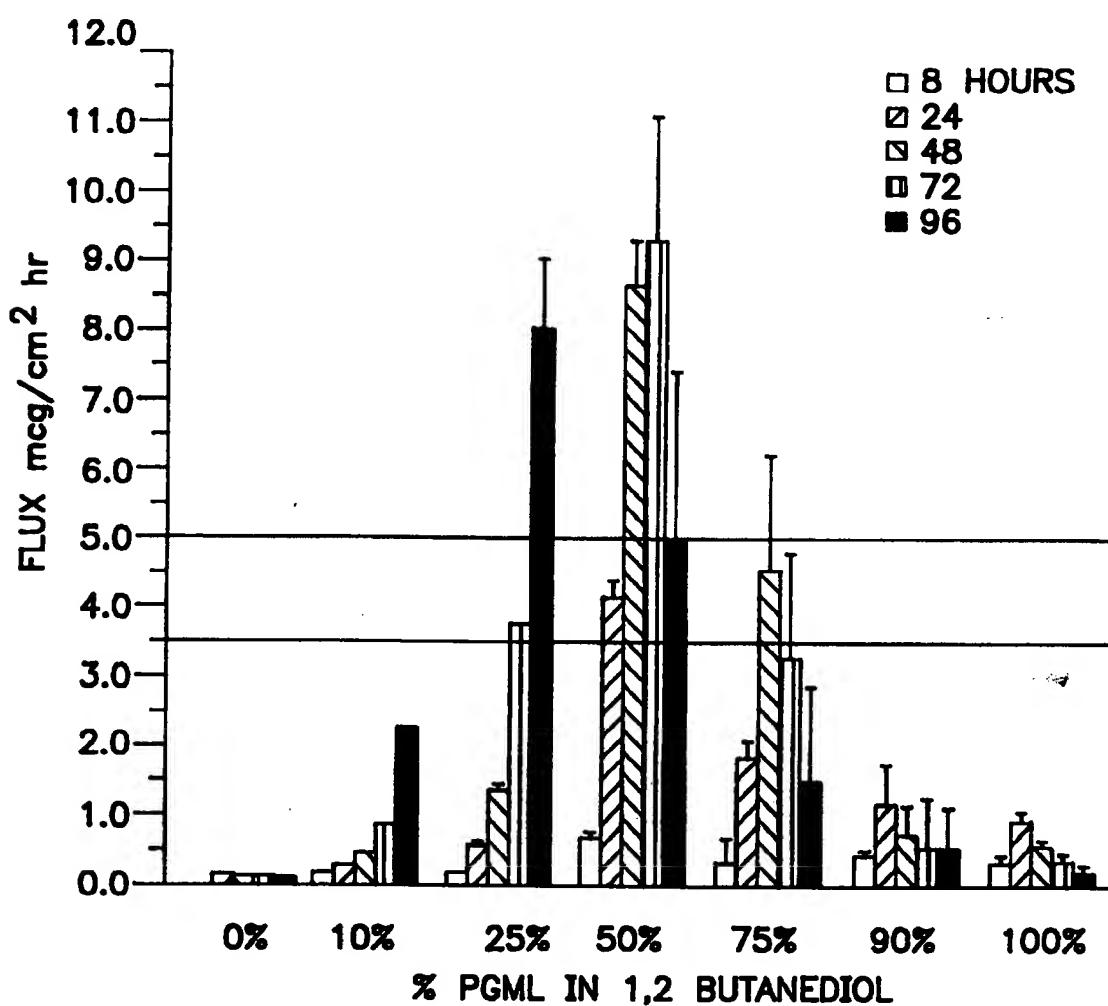


FIG. 4

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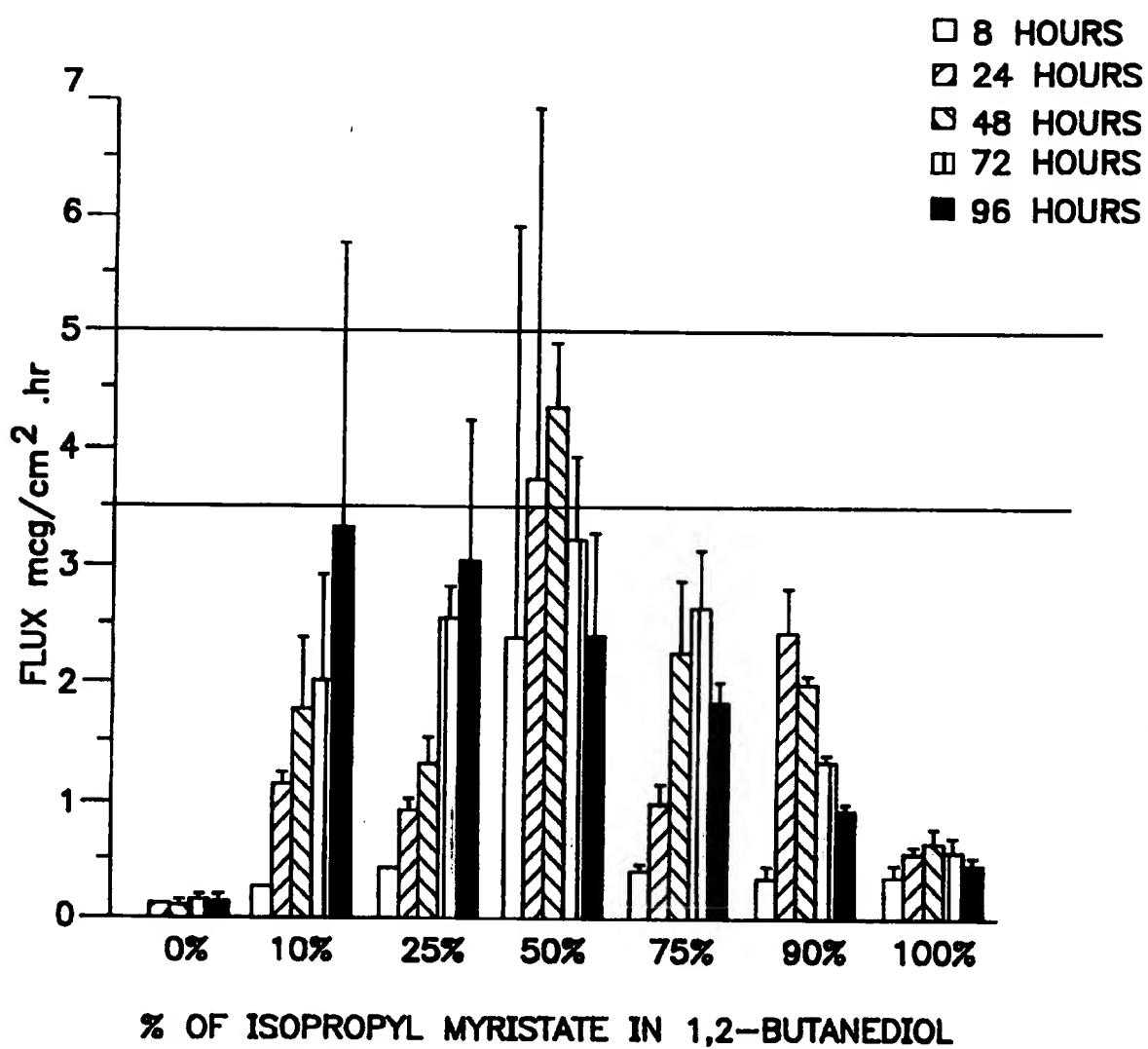


FIG. 5

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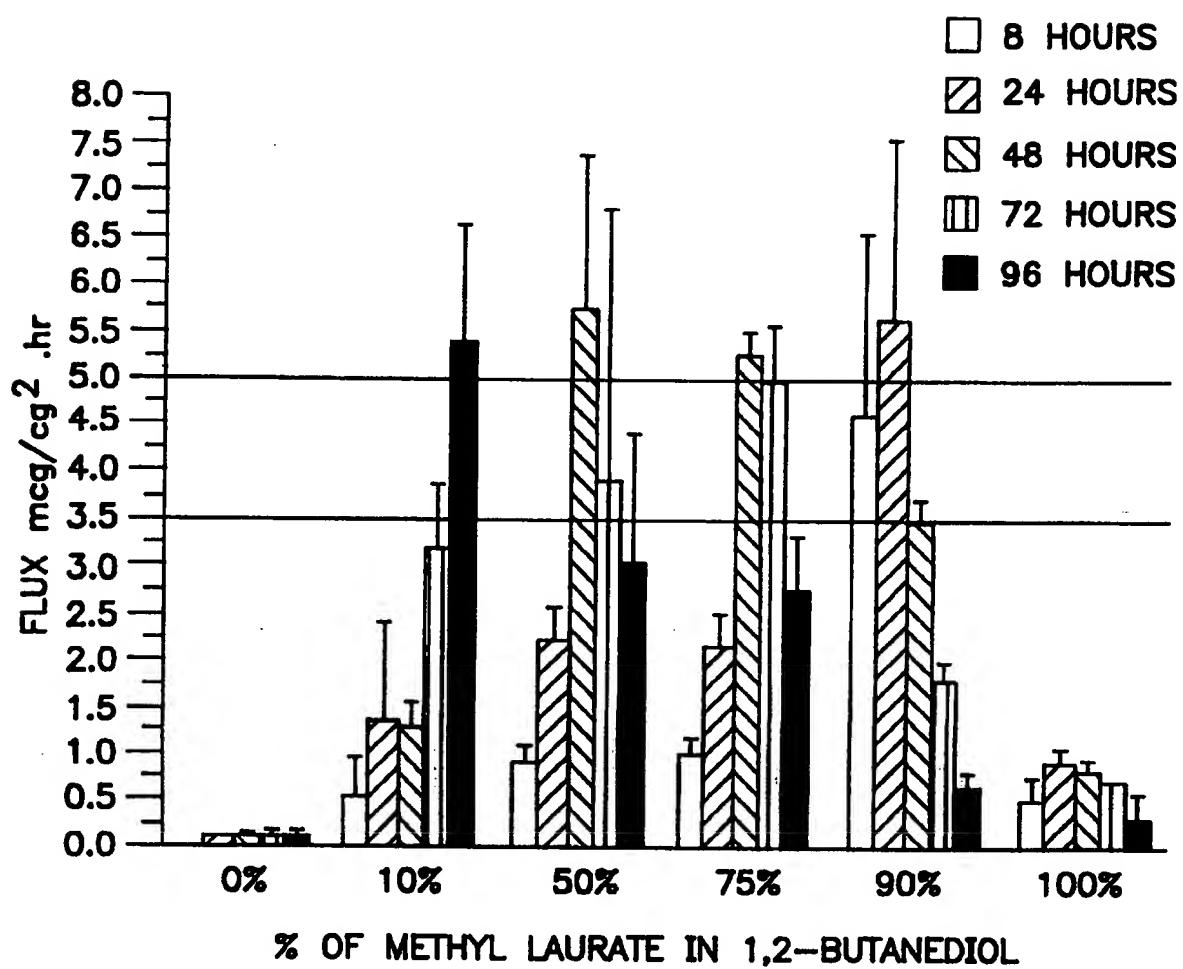


FIG. 6

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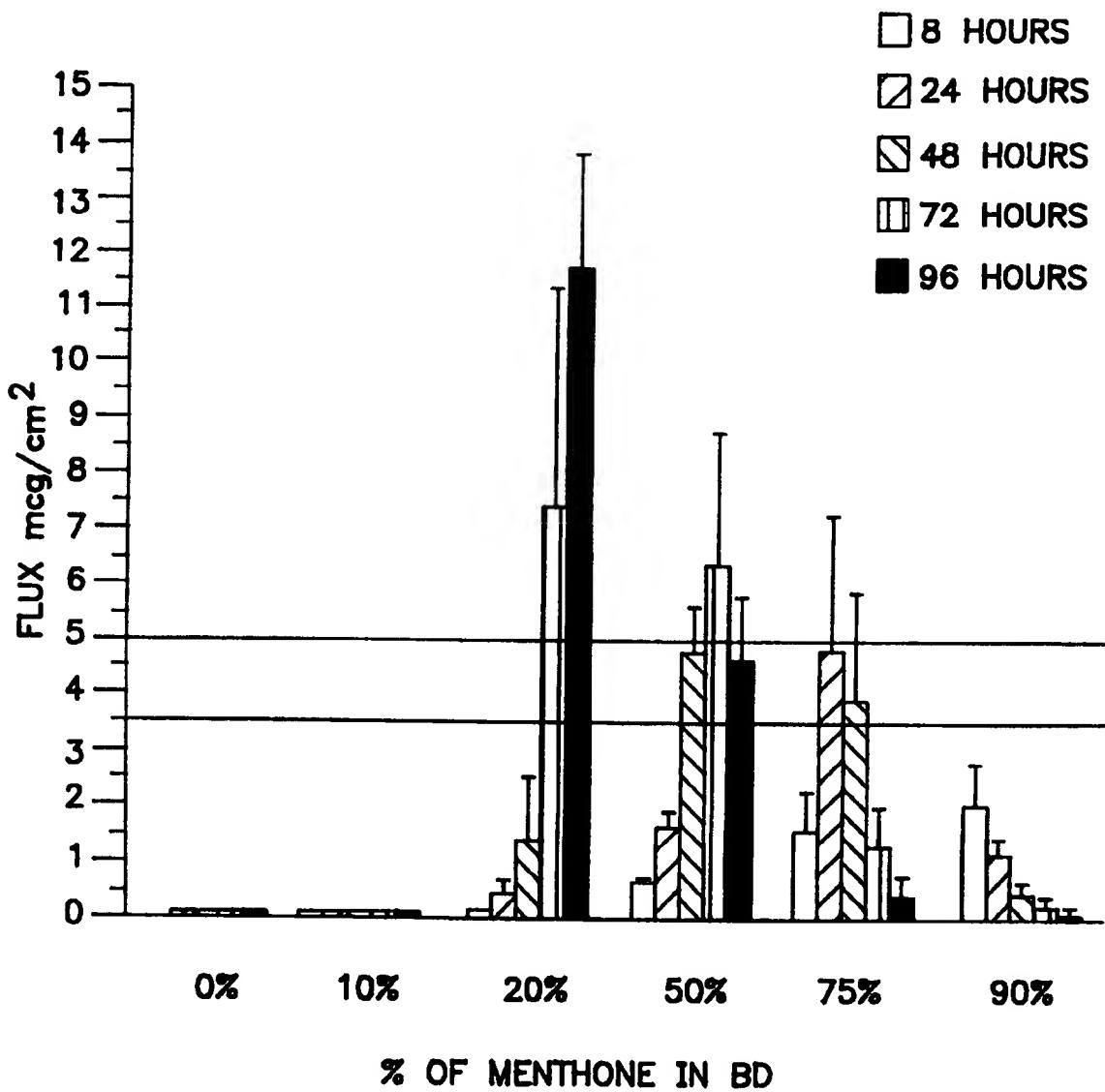


FIG. 7

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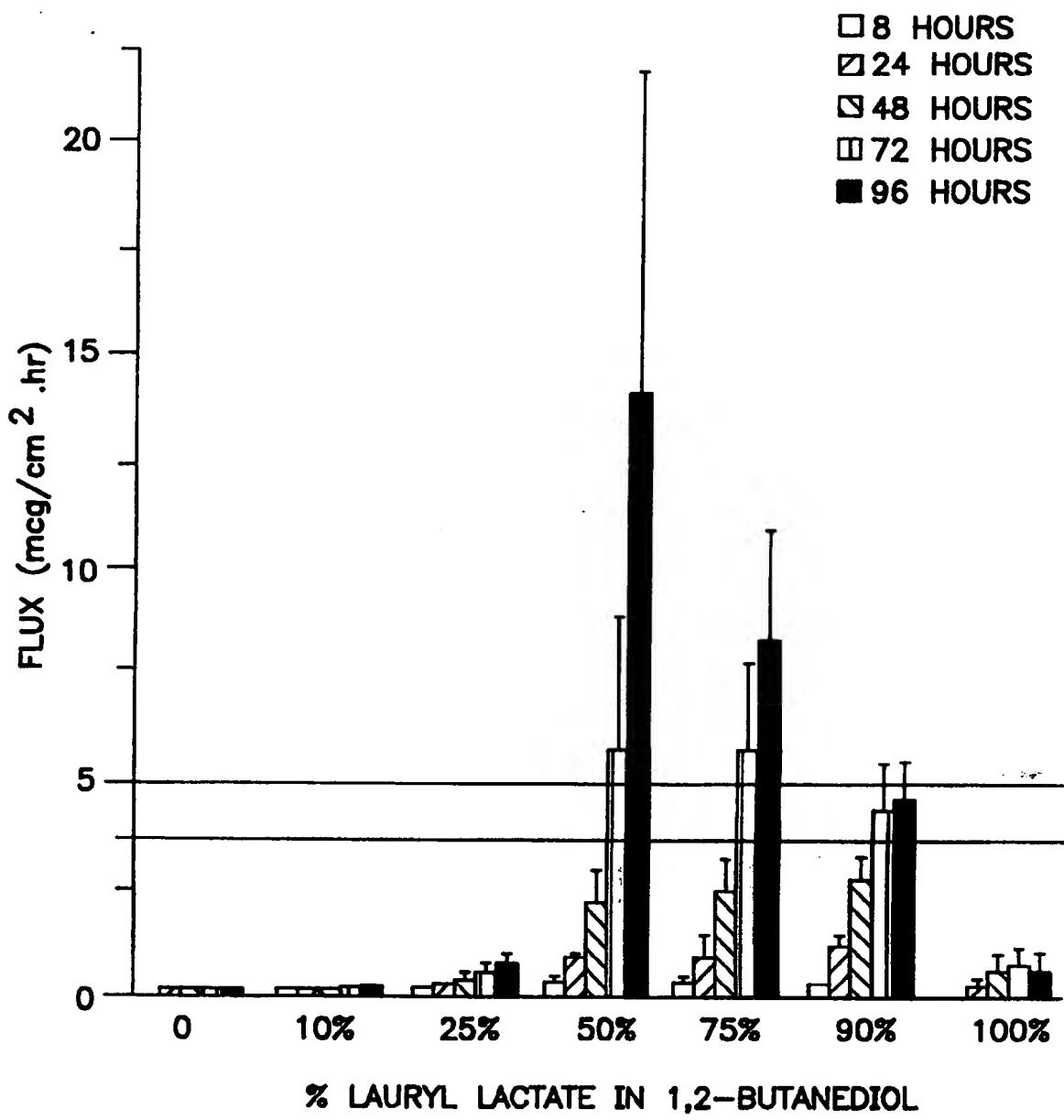


FIG. 8

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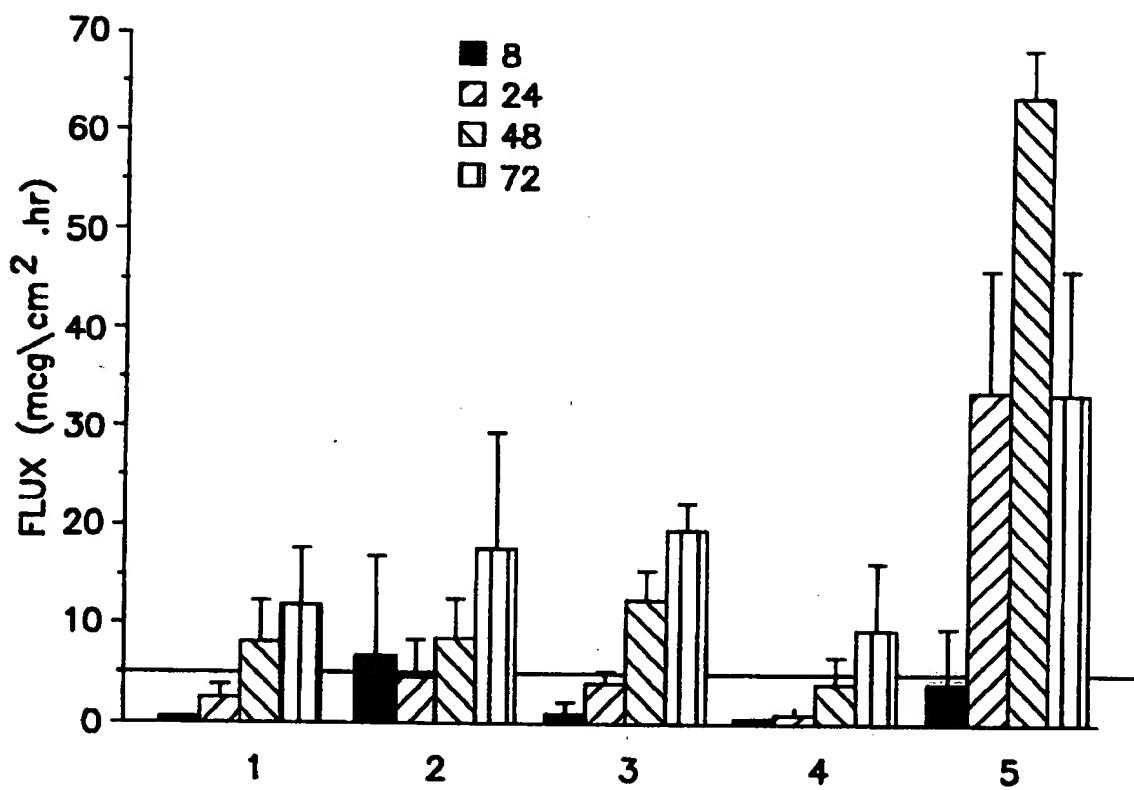


FIG. 9

8 / 11

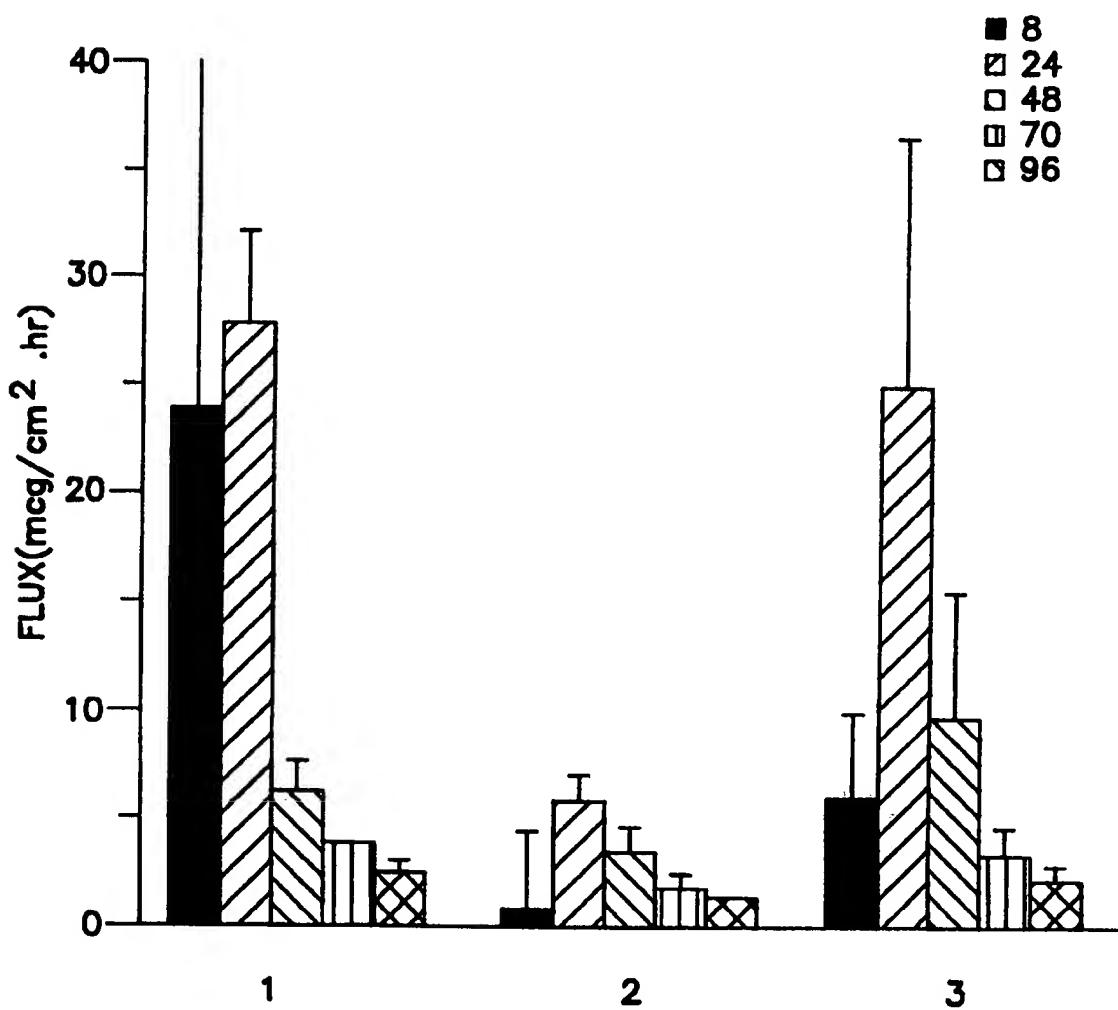


FIG. 10

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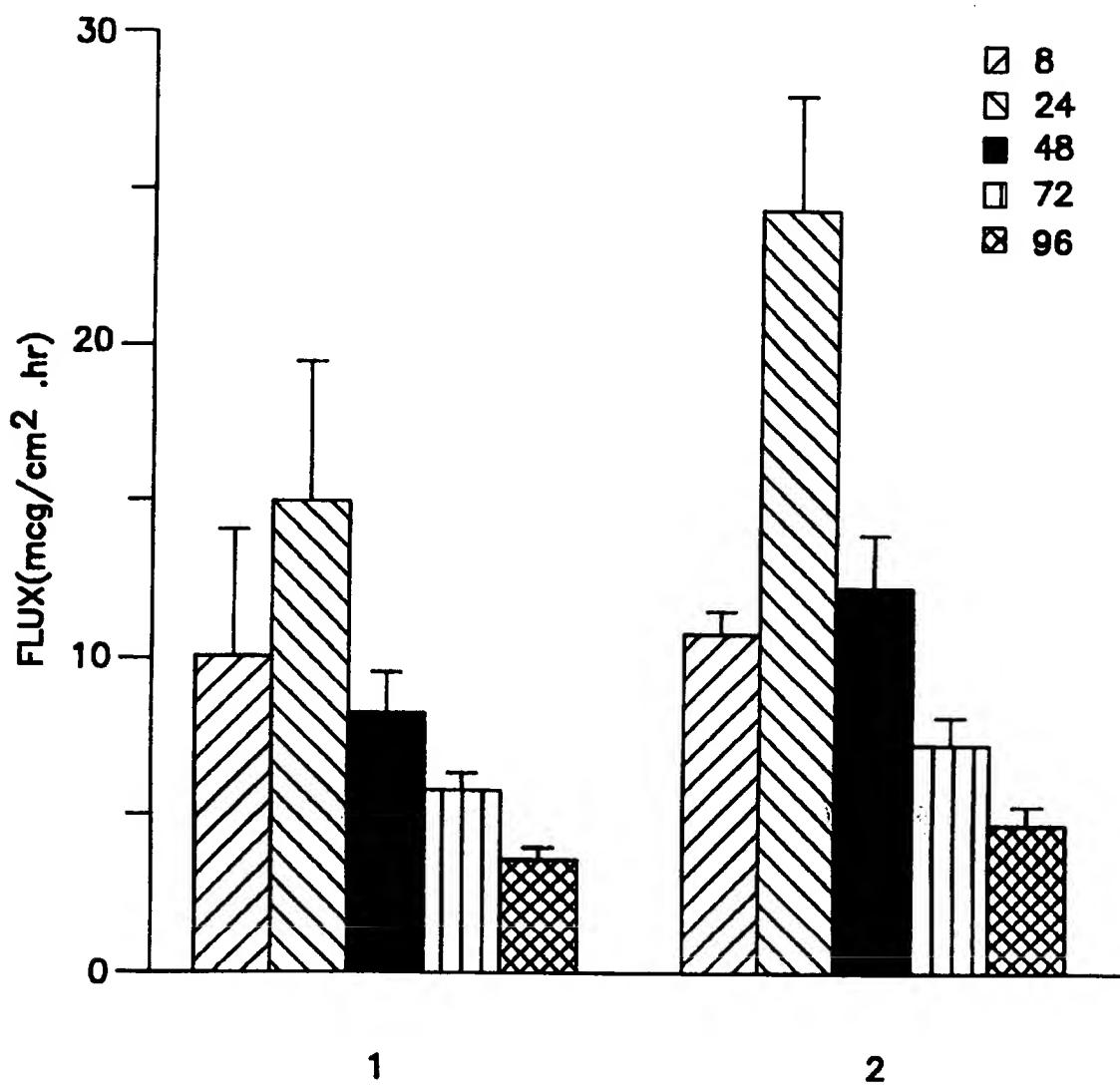


FIG. 11

10 / 11

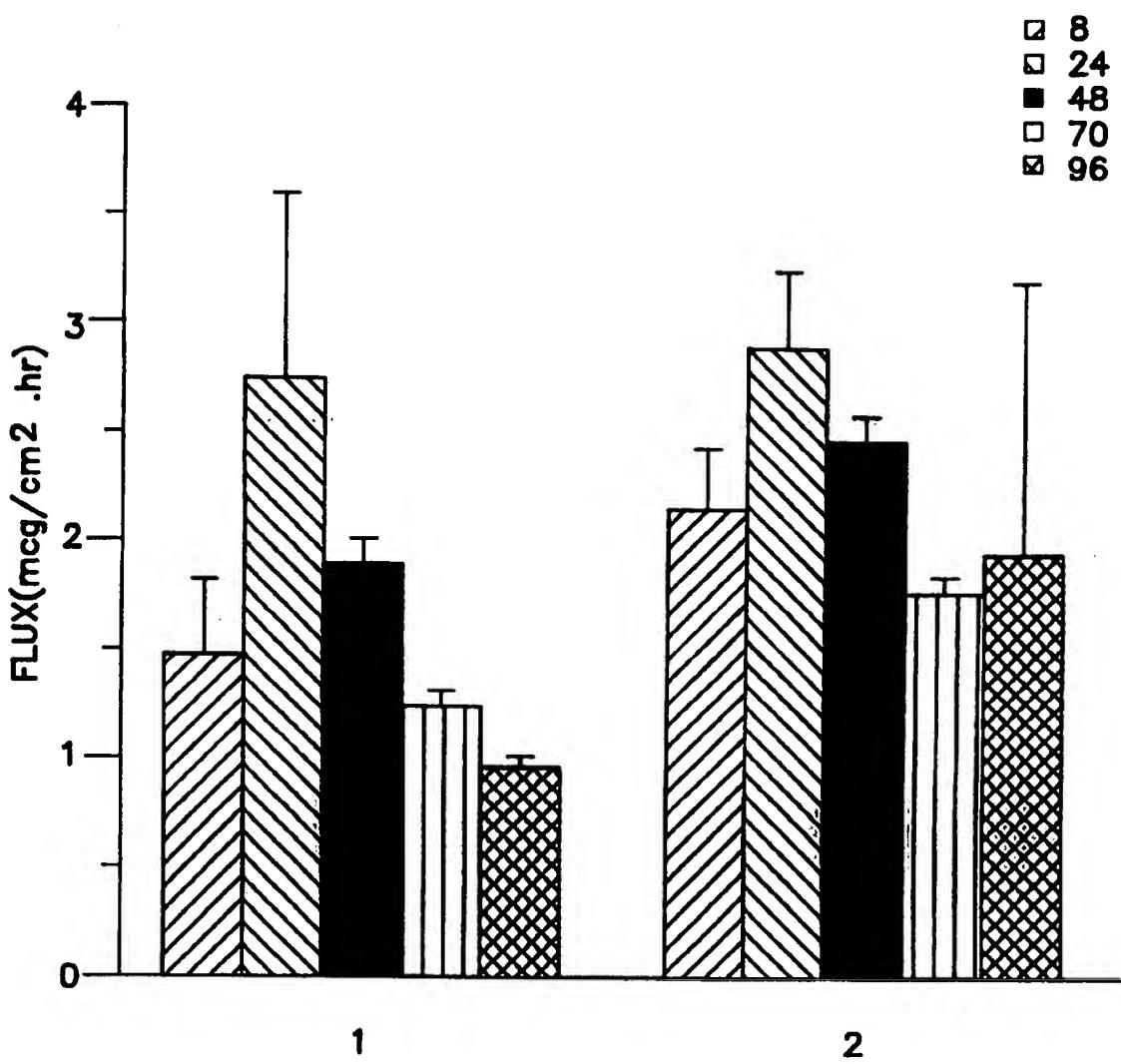


FIG. 12

11 / 11

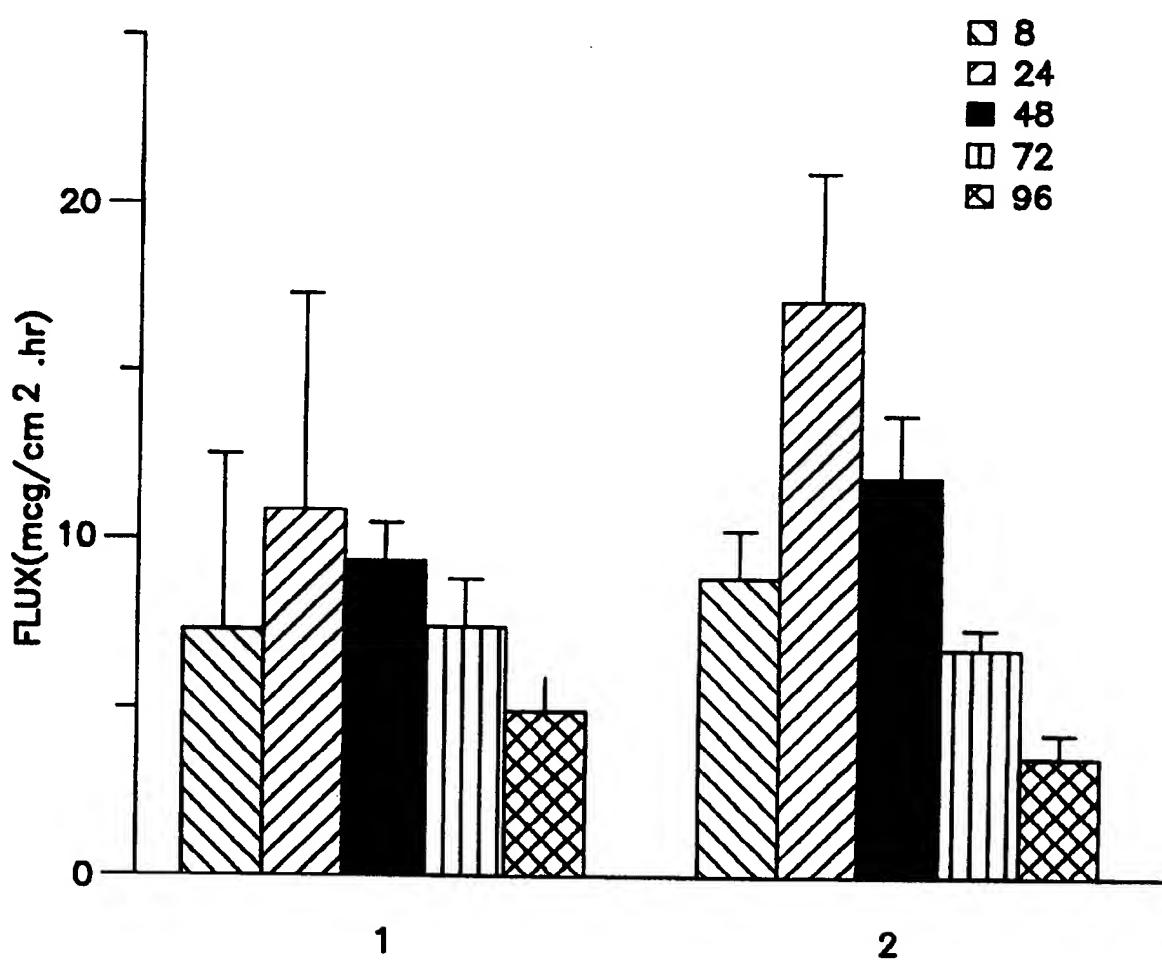


FIG. I3

# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 96/14713

**A. CLASSIFICATION OF SUBJECT MATTER**  
**IPC 6 A61K31/55 A61K9/70**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**IPC 6 A61K**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| A          | EP,A,0 454 436 (LILLY INDUSTRIES LTD.,UK)<br>30 October 1991<br>cited in the application<br>see claims<br>see page 7, line 34 - line 54<br>--- | 1-18                  |
| A          | EP,A,0 582 368 (LILLY INDUSTRIES LTD.,UK)<br>9 February 1994<br>see claims<br>see page 3, line 54 - page 4, line 18<br>---                     | 1-18                  |
| A,P        | US,A,5 457 101 (B. GREENWOOD ET AL.) 10<br>October 1995<br>see claims<br>see column 6, line 11<br>-----  | 1-18                  |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*V\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*A\* document member of the same patent family

2

Date of the actual completion of the international search

13 January 1997

Date of mailing of the international search report

23.01.97

Name and mailing address of the ISA

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Authorized officer

Scarpioni, U

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/14713

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-5

is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

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